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Computational Modeling of Vasculogenesis and Angiogenesis as Emergent Processes for the Design of Tissue Engineering Strategies

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1. Introduction

Vascularization is a key determinant of long-term viability, maturation, and functional integration in engineered tissues and regenerative scaffolds (Rouwkema, 2016). In the absence of a rapidly established microvascular network, oxygen and nutrient transport limitations lead to early hypoxia, impaired cell survival, and heterogeneous tissue growth. More broadly, vascularized tissue growth can be interpreted as the result of two complementary biological mechanisms.

The first mechanism is vasculogenesis-driven tissue remodeling, corresponding to the de novo self-organization of endothelial cells into primitive vascular networks within growing tissues or bioprinted constructs. This process is strongly regulated by extracellular matrix (ECM) composition, stiffness, and local biochemical signaling.

The second mechanism is angiogenic remodeling, corresponding to capillary sprouting and vascular ingrowth from a pre-existing artery, vein, or vascular pedicle inserted within or located near a scaffold. This mechanism is essential for long-term perfusion and can also contribute to the maturation of bioprinted constructs following the initial vasculogenesis phase.

The objective of this work is to develop a unified computational framework for vascularized tissue growth by coupling phase-field morphogenesis, reaction–diffusion transport, and agent-based endothelial migration, enabling the simulation of both de novo vascular formation and vessel-guided angiogenic remodeling.

This framework is largely adapted from the seminal work of Travasso et al., which we extend here to investigate vascular network emergence in controlled microenvironments relevant to tissue engineering applications.

2. Methods

A multiphase phase-field framework was developed to explicitly represent evolving tissue, vascular lumen, ECM, and scaffold domains.

The vascular phase is represented by a phase-field variable $\phi(X,t)$, where ϕ=1 denotes the endothelial phase and ϕ=0 the surrounding tissue. Its evolution is governed by an Allen–Cahn equation with VEGF-dependent stalk-cell proliferation (Travasso, 2011; Villanova, 2017):

$$\frac{\partial \phi}{\partial t} = -M_{vasc}\mu + \alpha_p T \phi \left(1 - \frac{\phi}{2}\right)$$

First term corresponds to the classical Allen-Cahn relaxation dynamics, with M the mobility of the phase and μ the derivative respective to ϕ of the free energy of the system. Second term is a logistic proliferative term modulated by a constant a_p and dependant of the local VEGF concentration field $T(x, t)$ governing endothelial activation and chemotactic migration.

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Angiogenic sprouting is driven by discrete tip cells modeled as Lagrangian agents whose position X_{tip} is given by:

$$\frac{dX_{tip}}{dt} = \chi \nabla T + \omega(\nabla T)\nabla\phi$$

The tip cells are guided by both VEGF-driven chemotaxis via VEGF gradient ∇T with sensitivity χ (first term) and by the vascular phase gradient $\nabla\phi$ modulated by weighting function $\omega = 0.4e^{-|\nabla T|/0.01}$ (second term). Thus, lack of VEGF gradient shifts growth guidance from chemotactic signalling toward attraction to pre-existing vascular structures creating anastomosis.

VEGF transport follows a reaction–diffusion equation:

$$\frac{\partial T}{\partial t} = D_{vegf}\nabla^2 T + (1-\phi)S_{vegf}(O_2) - \alpha_T T\phi$$

The equation is a classical reaction-diffusion equation where VEGF diffuses with the term $D_{vegf}\nabla^2 T$. Surrounding Tissue act as constant biochemical sources at rate $\propto_{vegf}$ which depends of tissue hypoxic state $S_{vegf}(O_2) = \propto_{vegf} if [0_2] < O_{2,treshold}$ Last term describes VEGF consumption by endothelial cells at rate α_T.

Finally, oxygen follows the same reaction -diffusion evolution as VEGF but with constant production by endothelial phase and consummation by tissue:

$$\frac{\partial O_2}{\partial t} = D_{O_2}\nabla^2 O_2 + \propto_{0_2} \phi - \alpha_{cell} O_2 (1-\phi)$$

This framework enables the simulation of two complementary scenarii:

1. vasculogenesis in bioprinted constructs, from homogeneous or aggregated endothelial cell distributions; (Fig 1- A)
2. angiogenic invasion from a pre-existing vessel, such as an artery or vein. (Fig 1 - C)

3. Results and discussion

Numerical simulations reproduce the emergence of primitive vascular networks through endothelial self-organization within 3D constructs. The phase-field formalism naturally captures lumen formation, branching, coalescence, and network maturation. Comparisons between homogeneous cell distributions, predefined aggregates, and intermediate partially constrained

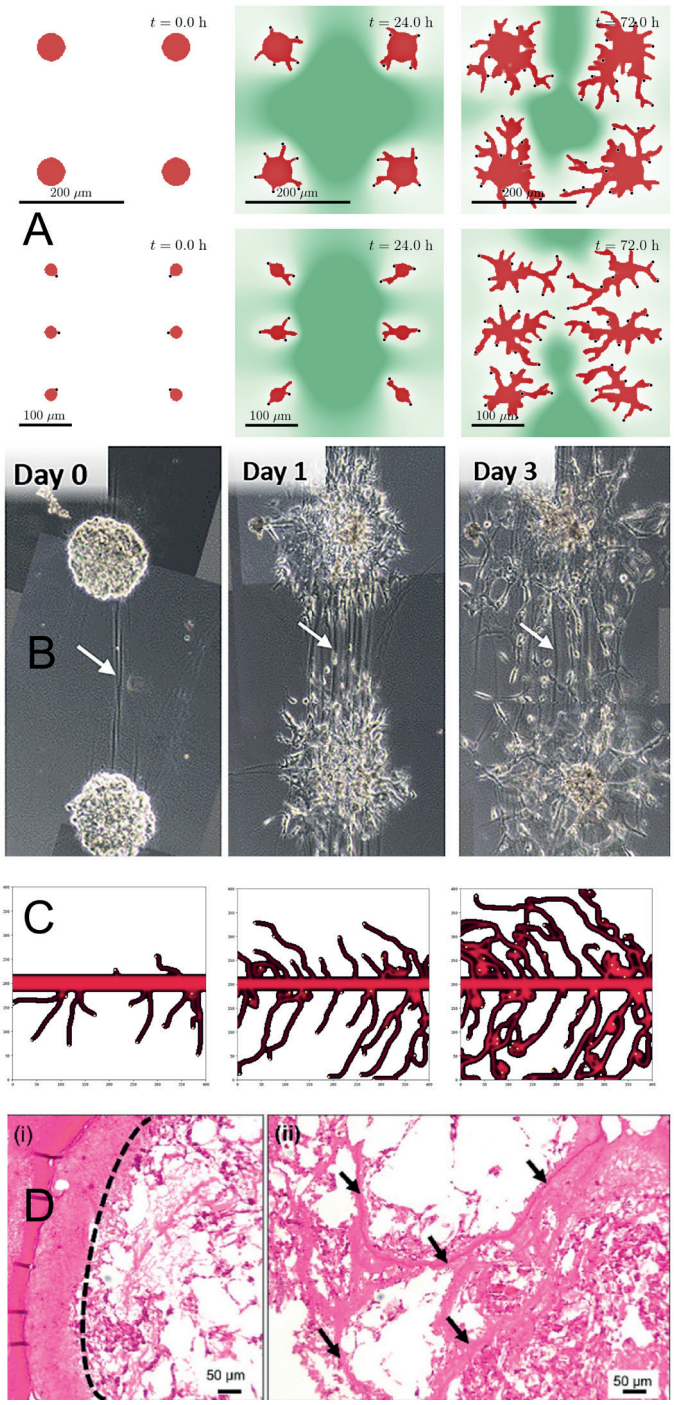

Figure 1. A) Phase-field simulation of vasculogenesis guided by agent-based tip migration (black dot) towards VEGF (green) B) in vitro vasculogenesis from deposition strategies of HUVEC aggregate in patches (Devillard, 2023) C)Angiogenesis simulation from a parent vessel D) Micro-vascularization in a 3D construct with co-cultured fibroblasts & HUVEC (Tröndle, 2019)

configurations reveal distinct morphogenetic dynamics. Fully self-organized configurations promote diffuse

vasculogenesis but may delay effective perfusion, whereas predefined aggregates accelerate lumen formation and early oxygen restoration. Intermediate strategies based on controlled aggregate size and spacing provide the best compromise between rapid vascular emergence and network adaptability (Fig 1-A). In a second scenario, angiogenic sprouting from a pre-existing vessel produces progressive capillary invasion toward hypoxic regions (Fig. 1-C). These models are able to reproduce vascular organization dynamics observed in vitro and in vivo (Fig. 1-B and 1-D). However, they remain incomplete, as certain biological phenomena are not yet taken into account, particularly vessel degradation or regression when the vascular network is not optimal for blood flow.

These findings support the interplay between de novo vascular self-organization and vessel-guided angiogenic remodeling.

4. Conclusions

This work presents a unified computational framework for vascularized tissue growth combining vasculogenesis and angiogenic remodeling. The model captures both de novo vascular self-organization and capillary invasion from pre-existing vessels, with potential applications in scaffold optimization, bioprinting, and predictive digital twins.

Contributor Roles

VT, JLM: Conceptualization, Methodology, Validation, Writing original draft, Writing – review & editing; JLM: Supervision, Funding acquisition, Writing – review & editing.

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